Opiate Dependence Treatments

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
buprenorphine sublingual tablets[1]	generic	Treatment of opiate dependence and is preferred for induction only.
buprenorphine/naloxone sublingual film (Suboxone®)[2]	Reckitt Benckiser	Treatment of opiate dependence
buprenorphine/naloxone sublingual tablets (Zubsolv®)[3]	Orexo, generic	Treatment of opiate dependence
naltrexone tablets (Revia®)[4]	Duramed, generic	Treatment of opiate dependence Treatment of alcohol dependence in conjunction with a behavior modification program
naltrexone extended-release injectable suspension (Vivitrol®)[5]	Alkermes	Prevention of relapse to opioid dependence, following opioid detoxification Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting

Reckitt Benckiser has discontinued brand Subutex® buprenorphine sublingual (SL) tablets as they believe the mono product (product containing buprenorphine alone without naloxone) creates a greater risk of misuse, abuse, and diversion.

On September 18, 2012, Reckitt Benckiser voluntarily discontinued brand Suboxone (buprenorphine and naloxone) SL tablets due to increasing concerns of pediatric exposure, based on a recent analysis on accidental pediatric exposures data from the U.S. Poison Control Centers.[6] The rates of Suboxone SL tablet were 7.8 to 8.5 times higher depending on the study period. Distribution of brand Suboxone SL tablets was formally discontinued on March 28, 2013. In July 2013, the FDA approved Zubsolv, buprenorphine and naloxone, SL tablets.

OVERVIEW

Although it may be the most publicized, heroin is not the only opiate that is abused. Prescription opiates such as oxycodone, morphine, and hydrocodone have become increasingly abused. The 2012 National Survey on Drug Use and Health (NSDUH) reported there was an estimated 23.9 million Americans 12 years and older who were current (past month) illicit drug users. Current illicit drug users were defined as Americans who have taken cocaine (including crack), marijuana/hashish, heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics non-medically within the month previous to the survey. The study also concluded there were 23.1 million Americans in need of substance abuse treatment. Of those patients only 2.6 million received treatment leaving approximately 20.5 million Americans still in need of substance abuse treatment.[7]

Methadone is a full opiate receptor agonist that has been thoroughly studied and is widely used as treatment for opiate dependence. It is orally active, can be dosed once daily, and can suppress symptoms of opiate withdrawal while blocking the effects of other opiates. Maintenance on methadone is generally safe. The most common adverse effects of methadone include constipation,

sexual dysfunction, and sweating. Methadone users are also subject to effects of long-acting opiates like respiratory depression.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act and has the same potential for abuse as other opioids. Both buprenorphine and buprenorphine/naloxone (Suboxone) can be used for office-based detoxification from opiates and maintenance treatment for opiate dependency by specially trained and registered physicians. Like methadone, buprenorphine can suppress opiate withdrawal symptoms and block the effects of other opiates. The American Psychiatric Association 2006 guidelines on the treatment of patients with substance abuse disorders suggest that buprenorphine may be best suited for patients with mild to moderate levels of physical dependence.[8] A formal evaluation of methadone is not within the scope of this review.

Under the Drug Addiction Treatment Act in order to become a qualified practitioner, physicians must be licensed under State law to practice medicine, obtain a waiver from the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), and notify the Secretary of Health and Human Services (HHS) of their intention of prescribing or dispensing buprenorphine. Such practitioners hold a modified Drug Enforcement Administration (DEA) registration, in which they are designated by a unique identifier and must include it on each prescription written.[9,10]

Oral naltrexone was approved in 1984 for the adjuvant treatment of patients dependent on opiate agonists. FDA approval of naltrexone for the treatment of alcoholism was granted in 1995.[11] The FDA approved Vivitrol, a once-monthly intramuscular naltrexone formulation for alcohol dependence in 2006, and then in 2010, Vivitrol was approved for the prevention of relapse to opioid dependence after opioid detoxification.

PHARMACOLOGY

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. It is postulated that patients receiving buprenorphine are likely to experience euthymia due to the partial agonist activity at the mu-opioid receptor and antagonist activity at the kappa-opioid receptor. Buprenorphine effects may be limited by a ceiling effect.

Naloxone is an antagonist at the mu-opioid receptor. Buprenorphine/Naloxone (Suboxone) was co-formulated in order to prevent patients from abusing buprenorphine in combination with other opiates.

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism. Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms such as histamine release.

PHARMACOKINETICS[12, 13, 14, 15, 16]

Drug	Bioavailability (%)	Protein Binding (%)	Half-Life (hours)	Metabolism (Active Metabolite)	Elimination (%)
buprenorphine	variable	96 (alpha, beta globulin)	31-35	N-dealkylation, glucuronidation (norbuprenorphine)	urine: 30 Feces: 69
naloxone	low	45 (albumin)	5-6.25	glucuronidation, N-dealkylation, reduction	N/A
naltrexone	variable 5-40	21-28	biphasic naltrexone: 1.1-10.3 6-β-naltrexol: 2.3-16.8	6β-naltrexol	primarily renal
naltrexone extended-release injectable suspension	low	21	5–10 days	6β-naltrexol, is mediated by dihydrodiol dehydrogenase	primarily urine

Although the pharmacokinetics of buprenorphine/naloxone tablets and film are similar, not all doses and dose combinations met bioequivalence criteria.

CONTRAINDICATIONS/WARNINGS[17, 18, 19, 20, 21]

Buprenorphine and buprenorphine/naloxone (Suboxone, Zubsolv) are contraindicated in patients who have been shown to be hypersensitive to buprenorphine. Buprenorphine/naloxone is also contraindicated in patients who have been shown to be hypersensitive to naloxone.

Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Like other opiates, buprenorphine may produce orthostatic hypotension in ambulatory patients.

Buprenorphine, like other potent opiates, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased.

Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opiate type, characterized by withdrawal upon abrupt discontinuation or rapid taper.

Buprenorphine has the same abuse potential as other opioids. Therefore prescribers should use caution when prescribing buprenorphine and consider its potential misuse, abuse, and diversion risk. Multiple refills should not take place in early therapy or without frequent patient follow-up visits.

Significant respiratory depression or death has been associated with buprenorphine, particularly by the intravenous route, when taken with benzodiazepines or other CNS depressants. Buprenorphine or

buprenorphine/naloxone should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Buprenorphine containing medications should be kept out of reach of children as buprenorphine can cause severe or fatal respiratory depression in exposed pediatric patients.

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the opiate-dependent population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. Measurement of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended.

Deaths have occurred in opioid naïve patients who received a 2 mg dose of buprenorphine sublingually for analgesia. Buprenorphine should not be used for analgesia. Due to the naloxone component, buprenorphine/naloxone is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opiate agonists such as heroin, morphine, or methadone.

Naltrexone is contraindicated in patients currently taking opioids, in addition to any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids. It is also contraindicated in patients with acute opioid withdrawal, physical dependence to opioids, liver disease, or a history of hypersensitivity reaction to naltrexone.

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses. Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis.

Risk Evaluation and Mitigation Strategies (REMS)

There is a buprenorphine-containing transmucosal products for opioid dependence (BTOD) REMS. A medication guide will be dispensed with each buprenorphine, buprenorphine/naloxone, and naltrexone extended-release injectable suspension prescription. Naltrexone ER injectable suspension is also subject to a communication plan. Other elements in place to ensure safe buprenorphine and buprenorphine/naloxone use include verification of safe use conditions and patient monitoring.

DRUG INTERACTIONS[22,23,24,25,26]

Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP3A4 inhibitors should be closely monitored and may require buprenorphine or buprenorphine/naloxone (Suboxone) dose adjustments.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving buprenorphine sublingually be monitored for signs and symptoms of opiate withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Patients receiving buprenorphine in the presence of other CNS depressants (including alcohol) may exhibit increased CNS depression.

Post-marketing reports have indicated the combination of buprenorphine and benzodiazepines have resulted in coma and death. In many of these cases buprenorphine was misused by self-injecting the medication. Physicians should use extreme caution if prescribing the medications together.

Patients taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PI) with buprenorphine should be monitored as dose adjustments of buprenorphine may be needed.

Patients taking naltrexone may not benefit from opioid-containing medicines. Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of naltrexone. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics. Concomitant use of disulfiram and oral naltrexone is recommended by manufacturers only if potential benefits justify the risk, as both drugs are potentially hepatotoxic.

For alcohol dependence, the safety profile of patients treated with naltrexone concomitantly with antidepressants was similar to that of patients taking naltrexone without antidepressants.

ADVERSE EFFECTS[27,28,29,30,31]

Drug	Headache	Abdominal Pain	Withdrawal Syndrome	Constipation	Nausea	Insomnia
buprenorphine	28-34 (22.4)	11.7 (6.5)	18.4-24 (37.4)	5-14 (2.8)	7-13.6 (11.2)	21.4-28 (15.9)
buprenorphine/ naloxone (Zubsolv SL tablets)	36.4 (22.4)	11.2 (6.5)	25.2 (37.4)	12.1 (2.8)	15 (11.2)	14 (15.9)
naltrexone extended-release injectable suspension (Vivitrol)	3 (2)	nr*	N/A	N/A	reported	6 (1)
naltrexone hydrochloride (Revia)	>10	>10	reported	<10	>10	>10

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

*abdominal pain not reported for opioid dependence data but reported for alcohol dependence.

The safety of Suboxone sublingual film is supported by clinical trials using buprenorphine sublingual tablets, buprenorphine and naloxone sublingual tablets (Suboxone) and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with Suboxone sublingual film. Few differences in the adverse event profile were noted among Suboxone sublingual film, Zubsolv sublingual tablets, buprenorphine sublingual tablets, and a buprenorphine ethanolic sublingual solution. The most common adverse event (greater than one percent) associated with Suboxone sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision. When used for treatment of opioid dependence, the most common adverse effects of naltrexone extended-release injectable suspension

were injection site reactions, hypertension, sleeplessness, toothache, inflammation of the nasopharynx, and liver enzyme changes. These occurred at a rate of ≥ two percent of patients.

SPECIAL POPULATIONS[32, 33, 34, 35, 36]

Pediatrics

The safety and effectiveness of buprenorphine or buprenorphine/naloxone (Suboxone, Zubsolv) in patients less than the age of 16 have not been established.

The safety and efficacy of naltrexone extended-release injectable suspension (Vivitrol), as well as naltrexone oral tab (Revia) have not been established in the pediatric population.

Pregnancy Category: All agents in this class are Pregnancy Category C.

Renal Impairment

When IV buprenorphine was administered to dialysis dependent patients and normal patients no difference in buprenorphine pharmacokinetics was observed. Caution is recommended in administering oral naltrexone to patients with renal impairment. Caution is recommended in administering naltrexone extended-release injectable to patients with moderate to severe renal impairment.

Hepatic Impairment

Dosage should be adjusted in this population, with patients monitored for symptoms of opiate withdrawal. Naltrexone carries a boxed warning for causing hepatocellular injury when given in excessive doses and is contraindicated in acute hepatitis or liver failure. Use of naltrexone should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Dose adjustment of naltrexone extended-release injectable is not required in mild to moderate hepatic impairment. Naltrexone extended-release injectable has not been evaluated in severe hepatic impairment.

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Due to extensive metabolism, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. Therefore, dosage should be adjusted and patients should be monitored for signs and symptoms of precipitated opioid withdrawal.

Geriatrics

The safety and efficacy of buprenorphine, naloxone, or naltrexone have not been studied adequately to determine if an older population would respond differently than younger patients. Prescribers should use caution when prescribing buprenorphine to older patients since they have greater frequency of decreased cardiac, hepatic, and renal function, have more concomitant diseases, and often take multiple drugs. Geriatric patients should be started at the lowest dose possible.

DOSAGES[37,38,39,40,41]

Drug	Dosing	Availability
buprenorphine SL tablets	**For the prevention of undue symptoms of opiate agonist withdrawal during induction of opiate agonist dependence treatment:** Adults and Adolescents ≥ 16 years: 8 mg buprenorphine sublingually on day 1, 16 mg buprenorphine sublingually on day 2, and then the patient should begin maintenance treatment. Dosage titration over 2 days rather than 3–4 days appears to result in greater treatment success. When used for maintenance dosing, adjustments should be made in increments or decrements of 2 to 4 mg to a dose that maintains a level of treatment which suppresses opioid withdrawal.	2 mg and 8 mg sublingual tablets
buprenorphine/naloxone SL film (Suboxone)	**For the maintenance of opiate agonist dependence treatment:** Adults and Adolescents ≥ 16 years: Following induction to opioid dependence treatment, a target dose of 16/4 mg buprenorphine/naloxone sublingually once daily is suggested; however, doses ranging from 4–24 mg/day of the buprenorphine component may be required. Titrate dosage in increments of 2–4 mg/day of buprenorphine to a dose that holds the patient in treatment and suppresses opiate withdrawal symptoms. Doses above 24 mg/day have not shown any added benefit.	2 mg/0.5 mg and 8 mg/2 mg sublingual films
buprenorphine/naloxone SL tablets (Zubsolv)	**For the maintenance of opiate agonist dependence treatment:** Adults and Adolescents ≥ 16 years: Following induction to opioid dependence treatment, a target dose of 11.4/2.8mg buprenorphine/naloxone (two 5.7/1.4mg tablets) sublingually once daily is suggested; however, doses ranging from 2.8mg/0.72mg buprenorphine/naloxone to 17.1mg/4.2mg buprenorphine/naloxone may be required. Titrate dose in increments of 1.4mg/0.36mg or 2.8mg/0.72mg of buprenorphine/naloxone to a dose that holds the patient in treatment and suppresses opiate withdrawal symptoms. Doses above 17.1/4.2mg/day of buprenorphine/naloxone have not shown to provide any additional clinical benefit.	1.4 mg/0.36 mg and 5.7 mg/1.4 mg sublingual tablets

Dosages (continued)

Drug	Dosing	Availability
naltrexone hydrochloride tablets (Revia)	**Opiate dependence** ▪ Induction of therapy for opiate cessation: – Initiate induction regimen after completion of opiate detoxification and verification patient is opiate free 25 mg initially; if no evidence of withdrawal initiate 50 mg (doses as low as 12.5 mg have been used initially-titrating by 12.5 mg daily until 50mg dose has been achieved) ▪ Maintenance of therapy for opiate cessation: – 50 mg daily following induction **Alcohol dependence:** ▪ 50 mg once daily (following verification that patient is opiate-free) ▪ Safety and efficacy established only in short-term (up to 12 weeks of therapy) – Before prescribing: Patients must be opioid free for a minimum of seven to ten days prior to initiation of therapy. Since absence of an opioid drug in the urine, is not a sufficient indication that a patient is opioid-free, a naloxone challenge test may be administered. If the challenge test is positive, do not initiate therapy. Repeat the test in 24 hours.	50 mg tablets (scored)
naltrexone extended-release injectable suspension (Vivitrol)	**For the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting and for the prevention of relapse to opioid dependence following opioid detoxification:** 380 mg IM every 4 weeks or once a month; inject into the gluteal muscle and alternate buttocks for each subsequent injection; patients must be opioid-free and should not be drinking alcohol at the time of therapy initiation	380 mg vial per 4 mL diluent

Buprenorphine and buprenorphine/naloxone (Suboxone, Zubsolv) are administered as a single daily dose. When taken sublingually, buprenorphine and buprenorphine/naloxone tablets have similar clinical effects. However, due to bioavailability, dosing adjustments are necessary for patients who switch between these two formulations (tablet to film or film to tablet). One Zubsolv 5.7/1.4 mg sublingual tablet provides equivalent buprenorphine exposure to one buprenorphine/naloxone (Suboxone) 8/2 mg sublingual tablet. To ensure accurate dosing, equi dosing transitions should be made using the tables in the package insert.

Buprenorphine contains no naloxone and may be preferred for use during induction therapy. Buprenorphine/naloxone may be the preferred medication for maintenance treatment during unsupervised administration.

Maintenance buprenorphine should be limited to those patients who cannot tolerate buprenorphine/naloxone (Suboxone, Zubsolv) due to naloxone hypersensitivity.

Buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and film should be placed under the tongue until they are dissolved; swallowing the tablets or film reduces the bioavailability of the drug.

Patients taking short-acting opiates or heroin should initiate buprenorphine therapy at least four hours after the patient last used opiates or (preferably) when early signs of withdrawal begin. For patients taking methadone or other long-acting opiates, there is little clinical experience to draw from in order to provide guidance.

The recommended dose of naltrexone injection is 380 mg delivered intramuscularly every four weeks or once a month. The injection should be administered by a health care professional as an intramuscular (IM) gluteal injection, alternating buttocks, using the carton components provided. The carton contains customized 1.5 or 2 inch needles; Vivitrol should not be injected using any other needle than the ones provided. If a patient misses a dose, the patient should be instructed to receive the next dose as soon as possible.

Pretreatment with oral naltrexone is not required before using naltrexone injection. No data are available for conversion from oral naltrexone or restarting treatment after discontinuation.

CLINICAL TRIALS

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials of FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no clinical studies available using naltrexone HCl tablets, buprenorphine/naloxone (Zubsolv) or the buprenorphine/naloxone film formulation.

buprenorphine (Subutex) and buprenorphine/naloxone tablets (Suboxone)

A multicenter, randomized, double-blind, placebo-controlled trial involving 326 patients with opiate addiction was conducted.[42] Patients were assigned to buprenorphine/naloxone 16 mg/4 mg sublingual tablets, buprenorphine 16 mg, or placebo given daily for four weeks. The primary outcome measures were the percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates. The trial was terminated early because buprenorphine/naloxone and buprenorphine alone were found to have greater efficacy than placebo. The proportion of urine samples that were negative for opiates was greater in the combination and buprenorphine-alone groups (17.8 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent, $p<0.001$ for both comparisons). The active-treatment groups also reported less opiate craving ($p<0.001$ for both comparisons with placebo). Rates of adverse events were similar in the active-treatment and placebo groups.

naltrexone extended-release injectable suspension (Vivitrol) and placebo

The efficacy of naltrexone extended-release injectable suspension in the treatment of opioid dependence was evaluated in a 24 week, placebo-controlled, multicenter, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification. Patients were treated with an injection every four weeks of naltrexone 380 mg or placebo.[43] Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Standardized, manual-based psychosocial support was provided on a bi-weekly basis to all subjects in addition to medication. The cumulative percentage of patients achieving each observed percentage of opioid-free weeks was greater in the naltrexone group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23 percent of subjects in the placebo group compared with 36 percent of patients in the naltrexone group from Week 5 to Week 24. A greater percentage of patients in the naltrexone group remained in the study compared to the placebo group.

A randomized, multicenter, double-blind, placebo-controlled, 24 week trial of 250 adult patients from Russia with opioid dependence disorder who had 30 days or less of inpatient detoxification and seven days or more off all opioids was conducted to assess the efficacy, safety, and patient-reported outcomes of naltrexone extended-release injectable suspension.[44] Patients were randomly assigned to naltrexone extended-release injection (n=126) or placebo (n=124). The primary endpoint was the response profile for confirmed abstinence during weeks 5 to 24, assessed by urine drug tests and self report of non-use. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. The median proportion of weeks of confirmed abstinence was 90 percent in the naltrexone group compared with 35 percent in the placebo group ($p=0.0002$). Patients in the naltrexone group self-reported a median of 99.2 percent opioid-free days compared with 60.4 percent for the placebo group ($p=0.0004$). The mean change in craving was -10.7 in the naltrexone group compared with 0.7 in the placebo group ($p<0.0001$). Median retention was over 168 days in the naltrexone group compared with 96 days in the placebo group ($p=0.0042$). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one patient in the naltrexone group ($p<0.0001$). Naltrexone extended-release injectable suspension was well tolerated.

SUMMARY

Buprenorphine products are effective therapies for the treatment of opiate dependence disorders. Clinically, naltrexone is used to help maintain an opiate-free state in patients who are known opiate abusers. Naltrexone extended-release injectable suspension is of greatest benefit in patients who take the drug as part of a comprehensive occupational rehabilitative program or other compliance-enhancing program. Unlike methadone or levo-alpha-acetyl-methadol (LAAM), naltrexone does not reinforce medication compliance and will not prevent withdrawal.

Patients with severe opiate dependence may be considered for methadone therapy.

REFERENCES

1 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
2 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
3 Zubsolv tablets [package insert]. New York, NY; Orexo; August 2013.
4 Revia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
5 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
6 Manufacturer communications. Received September 25, 2012.
7 Available at: http://store.samhsa.gov/product/Results-from-the-2012-National-Survey-on-Drug-Use-and-Health-NSDUH-/SMA13-4795. Accessed December 13, 2013.
8 Available at: http://psychiatryonline.org/guidelines.aspx. Accessed December 13, 2013.
9 Zubsolv tablets [package insert]. New York, NY, Orexo; August; 2013.
10 Available at: http://buprenorphine.samhsa.gov/data.html. Accessed December 13, 2013.
11 Available at: www.clinicalpharmacology.com. Accessed December 13, 2013.
12 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
13 Zubsolv tablets [package insert]. New York, NY; August 2013.
14 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
15 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
16 Revia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
17 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
18 Zubsolv tablets [package insert]. New York, NY; August 2013.
19 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
20 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
21 Revia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
22 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
23 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
24 Zubsolv tablets [package insert]. New York, NY; August 2013.
25 Revia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
26 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
27 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
28 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
29 Zubsolv tablets [package insert]. New York, NY; August 2013.
30 Revia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
31 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
32 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
33 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
34 Zubsolv tablets [package insert]. New York, NY; August 2013.
35 ReVia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
36 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
37 Subutex [package insert]. Richmond, VA; Reckitt Benckiser; December 2011.
38 Suboxone film [package insert]. Richmond, VA; Reckitt Benckiser; August 2012.
39 Zubsolv tablets [package insert].New York, NY; August 2013.
40 Revia [package insert]. Pomona, NY; Duramed Pharmaceuticals; October 2013.
41 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
42 Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003; 349(10):949-58.
43 Vivitrol [package insert]. Waltham, MA; Alkermes, Inc; July 2013.
44 Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial. Lancet. 2011; 377(9776):1506-13.